III. Remarks

A. Formal Matters

Applicants herein amend claim 44 for clarification purposes and amend claims 43-53 to provide a proper antecedent basis for each claim.

Applicants herein amend the paragraph beginning at page 183, line 1 of the specification to capitalize the trademark used therein. Applicants respectfully submit that the trademark used therein is "ULTRAFREE-MC" and not "Millipore" as stated by the Examiner in the prior Office Action dated November 11, 2000. Millipore is the manufacturer and, as such, there is no requirement that the name be capitalized.

Applicants herein amend the paragraph beginning at page 173, line 9 of the specification to capitalize the trademark used therein.

In view of the application as originally filed providing support for each of the amendments made herein, Applicants respectfully submit that no new matter has been added.

B. Patentability Rejections

1. The Rejections Under 35 U.S.C. §112, First Paragraph – Written Description -- Should be Withdrawn

At page 3 of the Final Office Action, the Examiner maintains the rejection of claims 44 and 46 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. Examiner alleges that the instant specification does not provide sufficient written description to show possession of the entire genus of binding pairs. Examiner alleges that the instant specification "only discloses examples of one type of specific binding pair, antibodies."

Applicants respectfully submit that Examiner has improperly construed the term "specific binding pair" and consequently has improperly construed claims 44 and 46. The instant specification describes a "specific binding pair" at page 27, line 23 through page 28, line 5 as follows:

> This describes a pair of molecules (each being a member of a specific binding pair) which are naturally derived or synthetically produced. One of the pair of molecules, has

> an area on its surface, or a cavity which specifically binds to, and is therefore defined as complementary with a particular spatial and polar organization of the other molecule, so that the pair have the property of binding specifically to each other. Examples of types of specific binding pairs are antigen-antibody, biotin-avidin, hormone-hormone receptor, receptor-ligand, enzyme-substrate, IgG-protein A.

The present invention relates to the display of a member of a specific binding pair, i.e., "a specific binding pair member." A "pair" is composed of two molecules, each of which binds the other. An antibody binds an antigen – thus antibody and antigen represent a specific binding pair. An antibody is a member of a specific binding pair, wherein the pair is composed of antibody and antigen. Similarly, an enzyme and substrate represent a specific binding pair. To act on its substrate an enzyme must bind that substrate. An enzyme is a member of a specific binding pair, wherein the pair is composed of enzyme and substrate. Similarly, a receptor and ligand represent a specific binding pair in which the receptor binds the ligand. The receptor is a member of a specific binding pair, wherein the pair is composed of the receptor and its ligand.

The instant application contains experimental exemplification of the display of a wide variety of members of different specific binding pairs. For example, the specification discloses the following specific binding pairs:

1) phage displayed anti-lysozyme VH domain is shown to form a specific binding pair with lysozyme. *See* Example 4;
2) various phage displayed antibody scFV domains are shown to form specific binding pairs with their respective antigens. *See* Examples 4, 6, 8, 9, 13, 18, 21, 23, 25, 29, 43 and 45;
3) phage displayed PDGF receptor (hereinafter "PDGF-R") are shown to form specific binding pairs with the ligand PDGF. *See* Examples 15 and 16;
4) phage displayed staphylococcal nuclease is shown to form a specific binding pair with its substrate, single stranded DNA. *See* Example 36;
5) either of two amino-terminal domains of phage displayed human CD4 are shown to form specific binding pairs with ligand gp120. *See* Example 37;

6) various phage displayed antibody Fab fragments are shown to form specific binding pairs with their respective antigens. *See* Examples 7, 25, 26, 27, 33 and 41; and

7) phage displayed alkaline phosphatase monomers are shown to form specific binding pairs with non-displayed alkaline phosphatase monomers (as measured by activity of the resulting dimer) See Examples 11, 12, 30, 31 and 32.

In each of the aforementioned cases, a specific binding pair member is displayed on the surface of a phage and demonstrated to form a specific binding pair with its respective complementary binding member.

Moreover, Applicants' use of the term "specific binding pair" is consistent with the ordinary and customary meaning of the term to one of ordinary skill in the art. Phage display provides a method for detecting protein-ligand interactions. For example, a population of proteins containing a protein of interest (one member of the binding pair) may be displayed on the surface of the bacteriophage particles and screened against a potential ligand (potential complementary member of the binding pair) in order to obtain a protein of interest which specifically binds to the ligand. (As an example, an enzyme of interest that binds a substrate can be obtained.) This is described at length throughout the specification, and illustrated schematically in Figure 2. One of ordinary skill in the art fully understands that displaying both members of a specific binding pair on the phage surface would defeat the purpose of phage display.

In view of the foregoing, which demonstrates the display of a wide variety of specific binding pair members, it is clear that one of ordinary skill in the art would know that Applicant was in possession of the invention as claimed, at time of filing the Application. Accordingly, Applicants hereby request that the rejection for lack of written description support be reconsidered and withdrawn.

2. The Rejections Under 35 U.S.C. §112, First Paragraph – Enablement – Should be Withdrawn

At page 7 of the Final Office Action, the Examiner maintains the rejection of claims 44 and 45 under 35 U.S.C. §112, first paragraph, for an alleged lack of

enablement. The Examiner bases this rejection on his allegation that "[t]he only examples provided in the specification are phage displaying antibodies." Further, the Examiner alleges that, aside from phage displaying antibodies, "no other examples" of binding pairs are provided by the specification. Applicants again point out to the Examiner that the present invention relates to the display of a member of a specific binding pair, i.e., "a specific binding pair member" and not "methods of displaying 'binding pairs' on phage surface" as stated by the Examiner at page 9 of the Final Office Action. As noted *supra*, the instant specification discloses phage displaying a broad range of specific binding pair members, each of which is shown to bind to their respective binding partner. Accordingly, each specific binding pair member is demonstrated to be functional, i.e., folded correctly so as to be able to bind the complementary other member of the specific binding pair.

At page 9 of the Final Office Action, the Examiner alleges that "[t]he success of displaying single chain antibodies (comprising binding pairs) does not automatically translate into successful displaying other binding pairs such as receptor-hormone pairs." The Examiner overlooks the fact that it is a member of a specific binding pair that is displayed, not both members of the pair. Moreover, the Examiner overlooks the fact that (in addition to the experimental exemplification of different antibody molecules and different enzymes) the specification contains specific experimental exemplification of two non-antibody receptors of different structure and character, namely PDGF-R and CD4. *See* Examples 15 and 16 for PDGF-R, with results shown in Figures 18, 19, 20 and 21, which confirm display of PDGF-R on the phage surface and its specific binding to its complementary specific binding pair member, PDGF isoform BB. *See* Example 37 for CD4, with experimental results shown in Figure 43, demonstrating display of CD4 on the phage surface and specific binding to its complementary specific binding pair member gp120. In each case, a receptor, CD4 or PDGF-R, is displayed on the phage surface and demonstrated to interact with ligands gp120 and PDGF isoform BB, respectively, to form a specific binding pair.

At page 10 of the Final Office Action, the Examiner alleges that the instant specification provides evidence that phage display cannot be easily generalized to other proteins. Specifically, the Examiner points to the specification, beginning at page 10,

line 9, which allegedly recites an example of an unsuccessful attempt to display bovine pancreatic trypsin inhibitor. Applicants respectfully submit that Examiner has misread the specification. In relevant part, the specification states that "the proposal was not shown to be operative." See instant specification, page 10, lines 12-13. The proposal was not shown to be inoperative either – in fact WO90/02809 contains no experimental evidence at all, only hypothetical conjecture. There is no statement that the display was unsuccessful. In contrast to the Examiner's allegation, a wide variety of displayed proteins is demonstrated experimentally in the instant specification, as well as their ability to bind a relevant complementary specific binding pair member, such as an antigen, ligand, or substrate. Accordingly, Applicants respectfully request that the rejection for lack of enablement be reconsidered and withdrawn

3. **The Rejections Under 35 U.S.C. §112, Second Paragraph Should be Withdrawn**

At page 10 of the Final Office Action, the Examiner rejected claims 44-53 as amended under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. Specifically, the Examiner alleges that it is unclear: (1) if each recombinant cell comprises one member of a binding pair or both members; (2) of what entity "a binding domain" is comprised; and (3) of what entity "genetic material" is comprised. While it is believed that the claims were already clear, Applicants herein amend claim 44 as follows: (1) the claimed recombinant host cells each harbor a nucleic acid that encodes a member of a specific binding pair; (2) the members of specific binding pairs (and clearly not the bacteriophage particles) comprise the "binding domain"; and (3) the term "genetic material" refers to that of the bacteriophage particle. Claims 43-53 are amended to provide a proper antecedent basis for each claim.

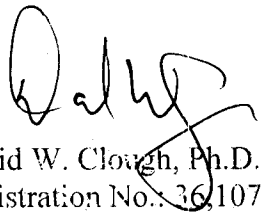
In light of the foregoing claim amendments and discussion Applicants respectfully submit that one of ordinary skill in the art would easily determine the metes and bounds of the claimed invention. Accordingly, Applicants request reconsideration and withdrawal of the rejection of claims 44-53 under 35 U.S.C. §112, second paragraph.

C. Conclusion

In view of the above amendments and remarks, Applicants respectfully submit that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the instant application, the Examiner is encouraged to call the undersigned at the number listed below.

Respectfully submitted,

HOWREY LLP

By: 

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